ELSEVIER

Determinants of Outcome after Endovascular Therapy for Critical Limb Ischemia with Tissue Loss

Andrew J. Meltzer, Gisberto Evangelisti, Ashley R. Graham, Peter H. Connolly, Douglas W. Jones, Harry L. Bush, John K. Karwowski, and Darren B. Schneider, New York, New York

Background: In this study we examine outcomes of endovascular therapy for critical limb ischemia with tissue loss and identify risk factors for failure of endovascular therapy across a panel of outcome metrics.

Methods: A retrospective review (2006–2010) of patients undergoing endovascular therapy for critical limb ischemia with tissue loss provided data for multivariate models of overall survival, amputation-free survival, limb salvage (LS), and wound healing.

Results: One hundred six patients underwent endovascular therapy for Rutherford class 5 (88%) or class 6 (12%) ischemia with ulceration and/or gangrene of the heel (15%), forefoot (16%), toe(s) (43%), calf/ankle (11%), or multiple locations (15%). Sustained limb salvage at 1 year was 87%. One-year overall survival and amputation-free survival were 65% and 49%, respectively. Multivariate regression models identified independent risk factors for reduced primary patency: Rutherford 6 ischemia ($P = 0.008$; HR 4.7 [95% confidence interval 1.5–14.8]) and infrapopliteal intervention ($P = 0.03$; HR 2.58 [95% CI 1.08–6.14]). Rutherford class 6 ischemia was independently associated with reduced assisted patency ($P = 0.004$; HR 5.39 [95% CI 1.74–16.73]). Wound healing was adversely affected by diabetes ($P = 0.02$; HR 7.0 [95% CI 1.4–36.2]), continued smoking ($P = 0.04$; HR 5.3 [95% CI 1.1–26.3]), and patency loss ($P = 0.04$; HR 4.8 [95% CI 1.1–22.30]). Rutherford class 6 ischemia was independently associated with reduced limb salvage ($P < 0.0001$; HR 35.1 [95% CI 5.4–231.2]) and amputation-free survival ($P = 0.007$; HR 3.61 [95% CI 1.4–9.18]), in addition to COPD ($P = 0.01$; 3.58 [95% 1.28–9.55]). Independent predictors of poor overall survival included end-stage renal disease ($P = 0.03$; HR 2.99 [95% CI 1.1–8.05]), history of angina ($P = 0.02$; HR 5.08 [95% CI 1.28–20.29]), and COPD ($P = 0.001$; HR 3.77 [95% CI 1.76–8.34]).

Conclusions: Both increasing severity of tissue loss as well as the presence of severe medical comorbidities are associated with poorer outcomes of endovascular therapy in these patients. Although sustained limb salvage in patients with tissue loss may be achieved with endovascular therapy, this is due to poor overall survival and a competing mortality hazard.

INTRODUCTION

Despite the widespread acceptance of endovascular therapy (ET) as a treatment option for peripheral arterial disease (PAD), surgical bypass with an autogenous saphenous vein conduit is generally considered the ''gold standard'' treatment to achieve limb preservation in patients with critical limb ischemia (CLI).[1,2] Although the durability of bypass surgery is superior to ET, the morbidity and mortality associated with major surgery warrant consideration of

Division of Vascular and Endovascular Surgery, Weill Cornell Medical College, New York–Presbyterian Hospital, New York, New York.

Correspondence to: Andrew J. Meltzer, MD, Division of Vascular and Endovascular Surgery, Weill Cornell Medical College, New York–Presbyterian Hospital, 525 East 68th Street, Payson 7, New York, NY 10065; E-mail: ajm9007@med.cornell.edu

Ann Vasc Surg 2014; 28: 144–151
http://dx.doi.org/10.1016/j.avsg.2013.01.018
© 2014 Elsevier Inc. All rights reserved.
Manuscript received: October 31, 2012; manuscript accepted: January 18, 2013; published online: September 5, 2013.

a minimally invasive approach in high-risk patients. Unfortunately, numerous reports have characterized the conundrum facing vascular specialists: many of the same comorbidities associated with adverse outcomes after surgical bypass are also associated with failure of ET.[3–5]

This is problematic for patients with the most severe ischemia, manifest as lower extremity ulceration or gangrene (Rutherford class 5 or 6). These patients have a particularly grim prognosis secondary to the end-organ effects of a severe atherosclerotic burden, and a high prevalence of severe comorbidities.[6] Although many reports have identified that the success of ET diminishes with more advanced disease, outcomes specifically in patients with tissue loss—and the risk factors for failure of ET—remain ambiguous.

The purpose of this study was to identify the factors associated with failure of endovascular therapy in patients with chronic CLI with tissue loss. Herein we describe our institutional experience with ET in this population, and identify risk factors for treatment failure with respect to several outcome metrics.

METHODS

Data Collection and Patient Selection

Patients undergoing primary endovascular intervention for chronic lower extremity ischemia from 2006 to 2010 were identified in a prospectively maintained database. This retrospective cohort study includes only those patients in whom ET represented the first effort at revascularization in the index limb. In all cases, procedures were performed by vascular surgeons; the decision to proceed with ET versus surgical bypass was made on a case-by-case basis. Patients undergoing diagnostic angiography only were excluded from the analysis. Indications for intervention included CLI with tissue loss, manifest as ulceration (Rutherford class 5) or gangrene (Rutherford class 6). Patients with acute limb ischemia were excluded. The institutional review board approved this retrospective review.

Operative reports and angiograms for endovascular cases were reviewed to determine lesion characteristics, procedural details, and runoff vessel status. Comorbidities were defined in accordance with accepted standards, as previously reported.[3,7,8] Given the limited applicability of the Trans-Atlantic Inter-Society Consensus (TASC) classification in the description of the severe pattern of disease described specifically in this study, the lesion lengths, presence of occlusions, and location of treated vessels are reported; these individual characteristics, rather than the composite TASC classification, were used in the development of multivariate models.

Procedural Technique

All interventions consisted of percutaneous transluminal angioplasty (PTA) with or without adjunctive stenting. Procedures were performed under local anesthesia with intravenous sedation in a hybrid operating room. Activated clotting time was maintained for >250 sec after administration of intravenous heparin, with 5F to 8F sheaths being used. Lesions were crossed by either an intraluminal or subintimal technique using hydrophilic guidewires (0.035, 0.018, or 0.014 inch). Choice of treatment modality (angioplasty with or without stent placement) was at the discretion of the operating surgeon.

Balloon angioplasty was performed with appropriately sized, noncompliant balloons, with inflation times ranging from 60 to 180 sec at 6–15 atm. Selective stenting in the femoropopliteal distribution was performed for residual stenosis >30% or presence of a flow-limiting dissection after angioplasty. Completion angiography with evaluation of the distal runoff was performed after all interventions. At postprocedure, all patients were maintained on dual antiplatelet therapy including lifelong aspirin and clopidogrel (75 mg) for 30 days, following a loading dose immediately after the procedure (300 mg).

Follow-up and Endpoints

Ankle–brachial indices (ABIs) and/or pulse volume recordings (PVRs) were obtained prior to interventions. Patients underwent scheduled follow-up at 1, 3, 6, and 12 months, and subsequently at annual intervals. Patency loss was noted by surveillance duplex ultrasound assessment of systolic velocity ratio elevation >2.5 in the treated segment relative to the immediately proximal arterial segment, or evidence of complete occlusion, with or without angiographic confirmation of patency loss. To permit accurate identification of failure time, interventions were considered to have failed at the earliest evidence of clinical, hemodynamic, angiographic, or duplex ultrasound–detected failure in accordance with established guidelines.[7,8]

For determination of limb salvage (LS) and amputation-free survival (AFS), major amputations (above the level of the ankle) were considered amputation events, whereas minor amputations at the digital or pedal level are included in calculations of debridements and other minor procedures. Wound healing refers to evidence of complete wound healing during the respective interval, and

was assessed and noted at 3-month intervals for 1 year after the index procedure.

Statistical Analysis

Comparisons of patient demographics and lesion characteristics between groups were made with χ^2 analysis, *t*-test, and Fisher's exact test, as appropriate. For time-dependent outcome measures (patency, limb salvage, overall survival, and amputation-free survival), factors associated with adverse outcome ($P < 0.1$) in univariate analysis were entered into multivariate Cox proportional hazards models to identify independent predictors of patency outcomes and limb salvage. Statistical models were constructed such that increasing hazard ratios represent an association with the adverse events. Therefore, increasing hazard ratios represent associations with reduced patency, LS, AFS, and OS. Models were tested for statistical significance and goodness of fit. All rates are reported using the Kaplan–Meier survival function, and comparisons were made with the log-rank test. $P < 0.05$ was considered statistically significant for all comparisons. All analyses were done using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

From 2006 to 2010, 106 patients, undergoing therapy in 109 limbs were treated with percutaneous transluminal angioplasty (PTA) as the primary treatment modality, with adjunctive stenting at the discretion of the operating surgeon.

Table I details patients' demographics, medical comorbidities, and treatment details for those patients undergoing ET. Of note, 67% of patients undergoing treatment were diabetic; 45% had evidence of chronic renal insufficiency, and an additional 17% were dialysis-dependent. The majority of patients undergoing ET had Rutherford class 5 ischemia (88.3%), and ulceration (80.9%) was more common than gangrene.

The majority of endovascular interventions included treatment of the SFA, with multilevel treatment commonly performed in the popliteal and/or tibial vessels. Adjunctive stenting was commonly performed in the treatment of iliac, femoral, and popliteal vessels; angioplasty was the predominant treatment modality in the infrapopliteal vessels, with ''bailout'' stenting in 6.4% of cases.

There were 3 (2.8%) perioperative mortalities within 30 days. The most common 30-day complications were early failure of the intervention (12%) and access-site complications, including hematoma and pseudoaneurysm (8%). All cases of return to the operating room (29%) were for wound care or subsequent minor or major amputation within 30 days. Three patients, all with Rutherford class 6 tissue loss, underwent major amputation within 30 days; review of these cases did not suggest that technical complications resulted in early limb loss.

For patients undergoing ET for TL, the association between risk factors for loss of primary and assisted patency, as well as delayed wound healing, by

Table I. Demographics, comorbidities, and treatment details

Demographics and comorbidities	
	N (%)
Male	51 (46.8)
Age, years (mean ±SD)	72.9 (±13)
Diabetes	73 (67.0)
Chronic renal insufficiency	49 (44.7)
End-stage renal disease	19 (17.0)
Hypertension	94 (86.2)
Hypercholesterolemia	53 (48.9)
Prior coronary bypass	27 (24.5)
Coronary artery disease	66 (60.6)
Congestive heart failure	38 (35.1)
Angina	3 (3.2)
Current smoker	12 (10.6)
Prior myocardial infarction	36 (33.0)
Chronic obstructive pulmonary disease	16 (14.9)
Tissue loss characteristics	
Gangrene	21 (19.1)
Rutherford class 6	13 (11.7)
Location	
Toe	44 (40.4)
Heel	15 (13.8)
Forefoot	16 (14.9)
Proximal	12 (10.6)
Multiple	15 (13.8)
Treatment details	
Femoral treated	79 (72.3)
Femoral stent	70 (63.8)
Femoral length, mm (mean ±SD)	119.6 (±124.7)
Popliteal treated	55 (50.0)
Popliteal stent	39 (36.2)
Popliteal length, mm (mean ±SD)	76.6 (±60.7)
Tibial treated	49 (44.7)
Tibial stent	7 (6.4)
Tibial length, mm (mean ±SD)	83.2 (±92.8)
Iliac treated	10 (9.6)
Iliac stent	10 (9.2)
Iliac length, mm (mean ±SD)	36.9 (±27.1)
Chronic total occlusion	83 (76.6)
Preoperative runoff: 0	8 (7.4)
Preoperative runoff: 1	71 (64.9)
Preoperative runoff: 2	3 (3.2)
Preoperative runoff: 3	5 (4.3)

Table II. Univariate analysis for patency and wound-healing outcomes

	Primary patency			Assisted patency			Wound healing		
	UHR	95% CI	*P*	UHR	95% CI	*P*	UOR	95% CI	*P*
Male	0.62	0.29–1.34	0.22	0.66	0.25–1.72	0.39	0.45	0.15–1.39	0.78
Age	0.84	0.33–2.19	0.73	0.81	0.24–2.71	0.74	0.83	0.22–3.03	0.49
DM	1.76	0.71–4.35	0.22	2.19	0.63–7.58	0.22	4.4	1.24–15.57	0.02
CRI	1.03	0.49–2.17	0.93	1.4	0.55–3.56	0.48	1.02	0.34–2.05	0.41
ESRD	1.11	0.38–3.23	0.85	1.1	0.31–3.87	0.89	0.66	0.17–2.61	0.62
HTN	0.36	0.10–1.26	0.11	2.05	0.46–9.17	0.35	0.46	0.08–2.61	0.46
Chol	1.84	0.83–4.11	0.14	1.9	0.67–5.43	0.23	1.79	0.589–5.42	0.31
CABG	1.5	0.68–3.30	0.31	2.41	0.88–6.57	0.09	0.46	0.13–1.58	0.21
CAD	2.3	0.99–5.32	0.05	3.03	0.97–9.44	0.06	1.15	0.37–3.58	0.82
CHF	2.32	1.03–5.21	0.04	1.31	0.49–3.50	0.6	0.59	0.19–1.83	0.36
Angina	0.4	0.05–3.00	0.37	0.05	0–490.8	0.6	0	0	1
Smoking	1.63	0.77–3.48	0.21	1.29	0.49–3.35	0.61	2.89	0.867–9.61	0.08
HxMI	0.55	0.26–1.18	0.13	2.14	0.84–5.42	0.11	1.19	0.37–3.80	0.78
COPD	0.94	0.22–3.98	0.93	1.87	0.42–8.29	0.41	3.75	0.66–21.5	0.14
Gangrene	14.4	1.37–151.0	0.03	1.88	0.65–5.42	0.24	1.07	0.21–5.33	0.94
R6	3.06	1.24–7.53	0.02	5.57	1.93–16.07	0	2.19	0.38–12.48	0.38
Toe									
Heel	4.83	1.60–14.58	0.01	0.46	0.05–3.77	0.47	3.42	0.39–7.05	0.42
Forefoot	3.54	1.12–11.16	0.03	2.02	0.54–7.40	0.29	3.33	0.74–15.68	0.11
Proximal	0.36	0.04–2.90	0.34	0	0	0.98	1.28	0.60–18.57	0.17
Multiple	10.12	3.01–33.97	<0.001	8.94	2.53–31.53	0	1.35	0.29–5.60	0.75
Fem	0.616	0.23–1.65	0.33	0.5	0.14–1.73	0.27	2.5	0.66–9.38	0.17
Fem stent	1.33	0.60–2.94	0.48	1.69	0.63–4.52	0.29	4.88	0.43–55.29	0.44
Pop	2.49	1.06–5.81	0.04	1.08	0.41–2.83	0.87	0.47	0.15–1.43	0.18
Pop stent	0.041	0–665.19	0.52	1.39	0.53–3.59	0.5	0.5	0.026–9.45	0.64
Tib	1.11	0.51–2.41	0.79	0.51	0.10–2.48	0.41	0.52	0.17–1.58	0.25
Tib stent	0.12	0–148.41	0.36	0.48	0.06–3.75	0.49	0	0	1
Iliac	0.902	0.12–6.72	0.92	0.67	0.09–5.11	0.7	1.29	0.16–9.90	0.81
CTO	1.191	0.55–2.60	0.66	1.88	0.72–4.92	0.2	1.24	0.80–1.92	0.33

UHR, univariate hazard ratio; UOR, univariate odds ratio; CI, confidence interval; DM, diabetes; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; HTN, hypertension; Chol, hypercholesterolemia; CABG, prior coronary bypass; CAD, coronary artery disease; CHF, congestive heart failure; HxMI, prior myocardial infarction; COPD, chronic obstructive pulmonary disease; Fem, femoral; Pop, popliteal; Tib, tibial; R6, Rutherford class 6; CTO, chronic total occlusion.

univariate analysis (including unadjusted hazard ratios and *P*-values) are shown in Table II. Risk factors for reduced limb salvage, amputation-free survival, and overall survival by univariate analysis are shown in Table III. For all analyses, an increasing hazard ratio (HR, or odds ratio) represents an increasing risk of adverse outcome. Development of multivariate regression models for each outcome metric identified those risk factors for failure (Table IV). Multivariate regression models identified independent risk factors for reduced primary patency: Rutherford class 6 ischemia ($P = 0.008$; HR 4.7 [95% confidence interval 1.5–14.8]) and infrapopliteal intervention ($P = 0.03$; HR 2.58 [95% CI 1.08–6.14]). Rutherford class 6 ischemia was independently associated with reduced assisted patency ($P = 0.004$; HR 5.39 [95% CI 1.74–16.73]). Wound healing was adversely affected by diabetes ($P = 0.02$; HR 7.0 [95% CI 1.4–36.2]), continued smoking ($P = 0.04$; HR 5.3 [95% CI 1.1–26.3]), and patency loss ($P = 0.04$; HR 4.8 [95% CI 1.1–22.30]). Rutherford class 6 category ischemia was independently associated with poorer limb salvage ($P < 0.0001$; HR 35.1 [95% CI 5.4–231.2]) and amputation-free survival ($P = 0.007$; HR 3.61 [95% CI 1.4–9.18]), in addition to chronic obstructive pulmonary disease (COPD; $P = 0.01$; HR 3.58 [95% CI 1.28–9.55]). Independent predictors of poor overall survival included end-stage renal disease (ESRD; $P = 0.03$; HR 2.99 [95% CI 1.1–8.05]), history of angina ($P = 0.02$; HR 5.08 [95% CI 1.28–20.29]), and COPD ($P = 0.001$; HR 3.77 [95% CI 1.76–8.34]).

At 1 year, primary patency was 64% and secondary patency was 72%. Limb salvage was 87%, which was sustained throughout long-term

Table III. Univariate analysis for limb and survival outcomes

	Limb salvage			Amputation-free survival			Overall survival		
	UHR	95% CI	*P*	UHR	95% CI	*P*	UOR	95% CI	*P*
Male	1.81	0.98–3.33	0.06	0.73	0.39–1.32	0.3	0.84	0.38–1.85	0.67
Age	1.33	0.66–2.68	0.42	0.92	0.43–1.95	0.48	0.62	0.33–1.16	0.13
DM	1.12	0.60–2.07	0.71	1.11	0.55–2.21	0.78	0.89	0.44–1.79	0.74
CRI	1.42	0.77–2.59	0.26	0.87	0.47–1.58	0.64	1.36	0.73–2.52	0.33
ESRD	0.78	0.38–1.58	0.49	1.4	0.67–2.92	0.37	7.14	1.46–34.79	0.02
HTN	2.76	1.16–6.53	0.02	3.3	1.53–7.09	0	4.99	2.24–11.10	<0.0001
Chol	1.05	0.58–1.90	0.87	0.97	0.53–1.78	0.92	1.28	0.68–2.37	0.44
CABG	0.77	0.39–1.53	0.45	1.15	0.57–2.35	0.69	1.09	0.52–2.29	0.82
CAD	0.82	0.45–1.50	0.51	1.37	0.75–2.53	0.31	1.17	0.63–2.18	0.61
CHF	2.22	1.17–4.21	0.02	1.86	1.02–3.37	0.04	1.84	0.99–3.38	0.05
Angina	3.51	0.81–15.23	0.09	2.06	0.63–6.69	0.23	4.5	0.98–20.58	0.05
Smoking	1.57	0.83–2.99	0.17	0.9	0.49–1.68	0.75	1.08	0.57–2.04	0.81
HxMI	0.98	0.51–1.89	0.95	1.1	0.57–2.13	0.77	1.08	0.55–2.12	0.82
COPD	1.98	0.87–4.50	0.1	2.53	1.23–5.22	0.01	3.05	1.18–7.49	0.02
Gangrene	1.93	0.79–4.72	0.15	0.58	0.30–1.14	0.11	1.87	0.41–8.5	0.42
R6	32	6.12–167.0	<0.0001	2.77	1.25–6.14	0.01	1.57	0.69–3.61	0.29
Toe									
Heel	3.76	1.13–12.5	0.03	0.68	0.22–2.10	0.5	2.48	0.99–6.19	0.05
Forefoot	0.5	0.126–1.99	0.33	0.51	0.16–1.62	0.26	1.66	0.62–4.55	0.33
Proximal	0.44	0.13–1.50	0.19	0.25	0.058–1.04	0.06	0.9	0.25–3.21	0.87
Multiple	0.37	0.097–1.43	0.15	2.68	0.85–8.44	0.09	2.91	1.19–7.13	0.02

UHR, univariate hazard ratio; UOR, univariate odds ratio; CI, confidence interval; DM, diabetes; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; HTN, hypertension; Chol, hypercholesterolemia; CABG, prior coronary bypass; CAD, coronary artery disease; CHF, congestive heart failure; HxMI, prior myocardial infarction; COPD, chronic obstructive pulmonary disease; Fem, femoral; Pop, popliteal; Tib, tibial; R6, Rutherford class 6; CTO, chronic total occlusion.

follow-up. Overall survival was 65% and 49% at 1 and 2 years, respectively. Amputation-free survival was 49% and 41%, respectively. Wound healing was 45% at 1 year. Complete longitudinal outcome data are presented in Figure 1, with accompanying life-table analysis shown in Table V.

DISCUSSION

Although many vascular specialists have adopted an ''endovascular first'' approach to the treatment of PAD, the optimal utilization of endovascular therapy versus bypass surgery remains unclear, particularly in patients with the most severe PAD. The Bypass versus Angioplasty for Severe Ischemia of the Leg (BASIL) Trial remains the only randomized, controlled study addressing this issue.[9] Results from this trial suggest no significant difference in OS and AFS based on first revascularization strategy overall; however, there was a statistically significant benefit associated with bypass surgery among those patients alive 2 years after randomization. These results must be interpreted with consideration given to the equipoise requirement for study inclusion, as well as other inherent differences between the study cohort and available treatment modalities in contemporary practice.[9,10]

Unfortunately, equipoise and cost considerations may limit future randomized studies, specifically among those patients with the most severe PAD. These patients, in whom disease is manifest as critical ischemia with ulceration or gangrene (Rutherford class 5 or 6), remain the group for which the selection of an ''optimal'' therapeutic strategy is most pressing. The need for adequate arterial perfusion to heal wounds must be balanced against the prevalence of comorbidities in this patient cohort, in whom surgical bypass may be associated with increased risk.

Prior reports detailing outcomes of endovascular therapy in PAD are notable for marked heterogeneity with respect to study population, particularly with respect to the severity of arterial disease burden. Institutional series and multicenter trials alike frequently include interventions performed for both claudication and CLI. The TASC guidelines offer some direction regarding the recommended use of endovascular therapy.[8] However, these guidelines tend to focus on femoropopliteal disease (where ET

Table IV. Factors associated with poor outcomes after endovascular therapy by multivariate analysis

	HR	95% CI	*P*-value
Reduced primary patency			
Rutherford 6	4.697	1.49–14.80	0.008
Infrapopliteal PTA	2.58	1.08–6.14	0.03
Reduced assisted patency			
Rutherford 6	5.392	1.738–16.731	0.004
Reduced wound healing			
Diabetes	7	1.4–36.22	0.02
Current smoking	5.3	1.1–26.3	0.04
Patency loss	4.8	1.1–22.30	0.04
Reduced limb salvage			
Rutherford 6	35.1	5.4–231.22	<0.0001
Reduced amputation-free survival			
Rutherford 6	3.61	1.40–9.18	0.007
COPD	3.58	1.28–9.55	0.01
Reduced overall survival			
ESRD	2.99	1.1–8.05	0.03
Angina	5.08	1.28–20.29	0.02
COPD	3.77	1.76–8.34	0.001

HR, hazard ratio; CI, confidence interval; PTA, percutaneous transluminal angioplasty; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease.

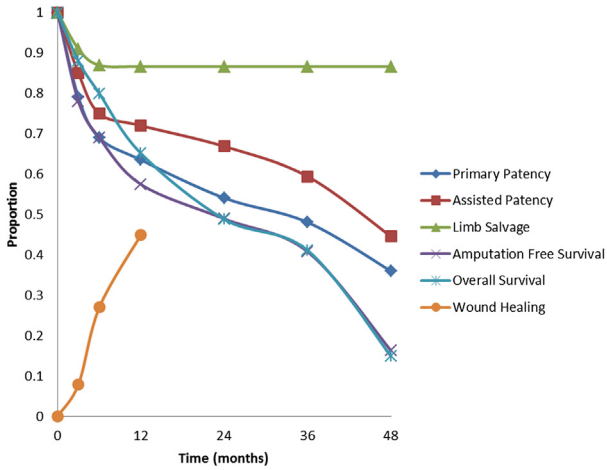

Fig. 1. Kaplan Meier estimates of outcomes of endovascular therapy for tissue loss.

is more accepted) and do not necessarily reflect the aggressive endovascular approach to the treatment of advanced disease now employed by many vascular specialists.

Chronic CLI itself represents a spectrum of disease, ranging from rest pain (Rutherford class 4) to extensive tissue loss (Rutherford class 6). Reports specifically addressing outcomes of endovascular therapy in this subgroup of patients with CLI and tissue loss are particularly lacking. Given the established impact of disease severity on outcome, the objective of our study was to identify the risk factors for failure of endovascular therapy, specifically in a population of patients with CLI and tissue loss (Rutherford class 5 or 6).

Established predictors of outcome after peripheral endovascular intervention include comorbidities, lesion characteristics, disease pattern, procedural details, patients' demographics, and indication for intervention (i.e., Rutherford classification).[8,11,12] Our data support these earlier reports; by univariate analysis, the severity of arterial disease was associated with patency loss and limb-based outcomes, whereas medical comorbidities were associated with reduced survival.

By multivariate regression, the severity of tissue loss (Rutherford class 6) was associated with reduced primary patency, assisted patency, limb salvage, and amputation-free survival. This finding is consistent with numerous prior reports that have identified the inverse correlation between the severity of ischemia and intervention patency, limb preservation, and survival-based outcomes.[5,13–17]

Wound healing was negatively affected by diabetes, continued smoking, and patency loss of the index intervention. Survival-based outcomes, including OS and AFS, were negatively affected by comorbidities, including COPD, ESRD, and angina; these findings are consistent with prior reports evaluating the association between comorbidities and survival after endovascular or open revascularization among patients with CLI.[14,18]

This study has further characterized the dismal prognosis associated with a diagnosis of CLI—particularly in the setting of tissue loss. The overall survival rates of 65% and 49%, at 1 and 2 years, respectively, observed in the current series are notably poorer than those observed in larger randomized trials.[9,19,20] This finding is not surprising, considering that patients with tissue loss may be expected to have an even more substantial burden of systemic atherosclerotic disease and associated comorbidities than the CLI population as a whole. Furthermore, the poor survival reflects an inherent treatment bias in our practice, which would favor utilization of an endovascular approach in those patients with the most severe comorbidities, in whom bypass surgery would be associated with increased perioperative risk—as opposed to the requirement for

Table V. Outcomes for endovascular therapy

	Interval (months)	Number entering interval	Number of terminal events	Proportion terminating in interval	Proportion surviving in interval	Cumulative survival	Standard error of cumulative survival
Primary patency	0–12	106	27	0.36	0.64	0.64	0.06
	12–24	15	2	0.15	0.85	0.54	0.08
	24–36	10	1	0.11	0.89	0.48	0.09
	36–48	7	1	0.25	0.75	0.36	0.12
Secondary patency	0–12	106	20	0.28	0.72	0.72	0.05
	12–24	17	1	0.07	0.93	0.67	0.07
	24–36	10	1	0.11	0.89	0.59	0.09
	36–48	7	1	0.25	0.75	0.45	0.15
Limb salvage	0–12	106	9	0.13	0.87	0.87	0.04
	12–24	20	0	0.00	1.00	0.87	0.04
	24–36	11	0	0.00	1.00	0.87	0.04
	36–48	9	0	0.00	1.00	0.87	0.04
Amputation- free survival	0–12	106	37	0.43	0.57	0.57	0.05
	12–24	31	4	0.15	0.85	0.49	0.06
	24–36	19	3	0.17	0.83	0.41	0.07
	36–48	14	6	0.60	0.40	0.16	0.07
Overall survival	0–12	106	30	0.35	0.65	0.65	0.05
	12–24	36	8	0.25	0.75	0.49	0.06
	24–36	20	3	0.16	0.84	0.41	0.07
	36–48	15	7	0.64	0.36	0.15	0.06
Wound healing	0–3	106	7	0.08	0.92	0.92	0.04
	3–6	60	9	0.15	0.85	0.73	0.05
	6–9	51	13	0.27	0.73	0.60	0.05
	9–12	39	2	0.05	0.95	0.55	0.05

clinical equipoise in larger trials.[14,18–20] Nonetheless, these sobering statistics likely reflect ''real-world'' outcomes of patients undergoing ET for CLI with tissue loss.

The influence of the competing mortality hazard on outcomes is apparent when one considers the disparity between amputation-free survival rates and limb salvage outcomes. By convention, mortality events are censored in limb salvage reporting. When the mortality rate is high—as is the case among patients with tissue loss—limb salvage rates may be somewhat misleading, as the mortality rate outpaces the actual event (i.e., amputation) rate. This phenomenon has obvious implications for the interpretation of clinical trials and other institutional series.

Limitations of this study include its retrospective, single-center design. The sample size is relatively small, although this is a consequence of the effort to specifically explore outcomes in a discrete subgroup of CLI patients. Furthermore, this series includes only those patients for whom endovascular therapy was favored over surgical bypass, a decision that was made on a case-by-case basis by the surgeon. This is an inherent limitation of such a retrospective cohort study.

Despite its limitations, we believe this study contributes to the ongoing effort to define the appropriate role of endovascular therapy in the treatment of PAD. For patients with CLI and tissue loss, we do believe that endovascular therapy should be considered in the setting of severe comorbidities that may prohibit bypass surgery. Excellent limb salvage outcomes in this population are less likely to result from interventional ''success,'' but rather from the striking effects of the competing mortality hazard. Finally, our findings quantify a conundrum facing vascular specialists: Many of the same comorbidities that support aggressive use of ET (by defining patients as ''high risk'') are also associated with endovascular treatment failures. Although endovascular therapy may be an option in select patients at high risk for surgical bypass, our results do not support an ''endovascular first'' approach for all patients with tissue loss.

REFERENCES

1. Arvela E, Venermo M, Söderström M, Albäck A, Lepäntalo M. Outcome of infrainguinal single-segment great saphenous vein bypass for critical limb ischemia is superior

to alternative autologous vein bypass, especially in patients with high operative risk. Ann Vasc Surg 2012;26:396–403.
2. Belkin M, Conte MS, Donaldson MC, Mannick JA, Whittemore AD. Preferred strategies for secondary infrainguinal bypass: lessons learned from 300 consecutive reoperations. J Vasc Surg 1995;21:282–93.
3. Meltzer AJ, Shrikhande G, Gallagher KA, et al. Heart failure is associated with reduced patency after endovascular intervention for symptomatic peripheral arterial disease. J Vasc Surg 2012;55:353–62.
4. Bakken AM, Protack CD, Saad WE, et al. Impact of chronic kidney disease on outcomes of superficial femoral artery endoluminal interventions. Ann Vasc Surg 2009;23:560–8.
5. O'Brien-Irr MS, Dosluoglu HH, Harris LM, Dryjski ML. Outcomes after endovascular intervention for chronic critical limb ischemia. J Vasc Surg 2011;53:1575–81.
6. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. J Vasc Surg 2010;51:230–41.
7. Ahn SS, Rutherford RB, Becker GJ, et al. Reporting standards for lower extremity arterial endovascular procedures. Society for Vascular Surgery/International Society for Cardiovascular Surgery. J Vasc Surg 1993;17:1103–7.
8. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral, Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(Suppl 1):S1–75.
9. Bradbury AW, Adam DJ, Bell J, et al. BASIL Trial Participants. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(Suppl.):5S–17S.
10. Conte MS. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg 2010; 51(Suppl.):69S–75S.
11. Haider SN, Kavanagh EG, Forlee M, et al. Two-year outcome with preferential use of infrainguinal angioplasty for critical ischemia. J Vasc Surg 2006;43:504–12.
12. DeRubertis BG, Faries PL, McKinsey JF, et al. Shifting paradigms in the treatment of lower extremity vascular disease: a report of 1000 percutaneous interventions. Ann Surg 2007;246:415–22.
13. Meltzer AJ, Graham A, Connolly PH, et al. Risk factors for early failure after peripheral endovascular intervention: application of a reliability engineering approach. Ann Vasc Surg 2013;27:53–61.
14. Dosluoglu HH, Lall P, Harris LM, Dryjski ML. Long-term limb salvage and survival after endovascular and open revascularization for critical limb ischemia after adoption of endovascular-first approach by vascular surgeons. J Vasc Surg 2012;56:361–71.
15. Khan MU, Lall P, Harris LM, Dryjski ML, Dosluoglu HH. Predictors of limb loss despite a patent endovascular-treated arterial segment. J Vasc Surg 2009;49:1440–5.
16. Dosluoglu HH, Lall P, Cherr GS, Harris LM, Dryjski ML. Superior limb salvage with endovascular therapy in octogenarians with critical limb ischemia. J Vasc Surg 2009;50: 305–15.
17. Taylor SM, York JW, Cull DL, Kalbaugh CA, Cass AL, Langan EM 3rd. Clinical success using patient-oriented outcome measures after lower extremity bypass and endovascular intervention for ischemic tissue loss. J Vasc Surg 2009;50:534–41.
18. Schanzer A, Mega J, Meadows J, Samson RH, Bandyk DF, Conte MS. Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data. J Vasc Surg 2008;48:1464–71.
19. Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: a multicenter, randomized, trial of edifoligide for the prevention of vein graft failure in lower extremity, bypass surgery. J Vasc Surg 2006;43:742–51.
20. Benoit E, O'Donnell TF Jr, Kitsios GD, Iafrati MD. Improved amputation-free, survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. J Vasc Surg 2012;55:781–9.